RESTRICTIVE LUNG DISEASES AND PULMONARY VASCULAR DISEASE

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INTRODUCTION
This lecture will discuss basic concepts, etiologic factors, pathologic features, pathogenesis, and clinicopathologic findings in the different types of interstitial lung diseases. It also will touch briefly on pulmonary vascular diseases.

LEARNING OBJECTIVES:

- Acute respiratory distress syndrome (ARDS) (BP, pp. 460-461)
  - Define ARDS and list common causes
  - Illustrate the mechanism of lung injury in ARDS and the role of proinflammatory and anti-inflammatory mediators
  - Describe the morphologic features of ARDS. Understand how they evolve, and know what happens if the patient survives.
- Diffuse interstitial lung disease (BP, pp. 472-474, 480-482)
  - List the major forms of diffuse interstitial lung diseases discussed
  - Be able to identify classic morphologic features of common interstitial lung diseases.
  - Recognize the major causes of pneumoconioses (BP, pp. 474-478)
  - Delineate the gross and microscopic features resulting from exposure to coal dust, silica, organic/animal dust, and asbestos.
  - Sarcoidosis (BP, pp. 478-480)
    - Define sarcoidosis
    - List the most common organs involved, and describe the characteristic histologic lesion
    - Describe the radiographic, gross, and histologic appearance of lesions in the hilar lymph nodes and lungs
- Define primary pulmonary hypertension. Recognize the characteristic histologic finding (plexogenic arteriopathy) (BP, pp. 484-485)

SUPPLEMENTAL READING (ROBBINS)
Basic Pathology, 9th edition, pp. 460-461, 472-485
Pathologic Basis of Disease, 8th edition, pp. 680-682 and 693-710

TERMS INTRODUCED IN THE LECTURE:
Adult respiratory distress syndrome (ARDS)
Hypersensitivity pneumonitis
Idiopathic pulmonary fibrosis
Obstructive and restrictive lung disease
Pneumoconioses
Pulmonary hypertension
Sarcoidosis

MAJOR CONCEPTS INTRODUCED IN LECTURE

RESTRICTIVE LUNG DISEASE

General concepts

In restrictive lung disease, the key abnormality is impaired airway filling due to decreased elasticity (fibrosis) of pulmonary parenchyma, resulting in reduced total lung capacity, while airflow is normal or reduced proportionately. Restrictive lung disease is characterized by reduced lung expansion and decreased total lung capacity. Normally the alveolar septa are extremely thin, composed of mainly elastic fibers. This allows the alveolar sacs to stretch during inspiration. In interstitial lung diseases there is fibrosis in the interstitium, which makes the septa stiff. This pathologic rigidity limits inspiratory volume and can increase effort required for inspiration. Fibrosis of alveolar walls also causes decreased gas exchange. DLCO (Diffusing capacity of the Lung for Carbon Monoxide) is low. Note that the FEV1/FVC is usually normal (>80%) in purely restrictive lung diseases. Unfortunately, in actual practice it's not uncommon for patients with restrictive lung disease to also have some degree of obstructive lung disease and this can complicate both diagnosis and treatment.

Restrictive lung disease can be divided into "acute" and "chronic" forms.

Acute respiratory distress syndrome (ARDS)

Introduction

Acute respiratory distress syndrome (ARDS) is clinically characterized by rapidly progressive respiratory failure, typically within 24-48 hours following an initiating event. Profound hypoxemia is typically present, with nearly all patients requiring mechanical ventilation. ARDS represents runaway acute lung injury that is usually fatal without intensive treatment. The pattern of changes that the pathologist sees microscopically is known as Diffuse Alveolar Damage (DAD).

Common Causes

A large number of conditions could result in ARDS. The main causes are:

1. Sepsis (most common)
2. Diffuse pulmonary infections/ pneumonia
3. Gastric aspiration
4. severe mechanical trauma with shock (head injuries)
5. Acute Pancreatitis

- Acute interstitial pneumonia / Hamman-Rich Disease is a clinicopathologic term used to describe ARDS of undetermined etiology.

Pathogenesis

The basic pathology is thought to be an imbalance between proinflammatory (IL-1, IL-8, TNF) and anti-inflammatory mediators (IL-10, antiproteases) leading to accumulation of alveolar neutrophils and macrophages. A possible role for the NF-kB pathway is suggested in a shift towards an uncontrolled proinflammatory state (ref to fig 13-3 of BP). Alveolar macrophages release cytokines, that are chemotactic to neutrophils. Activated neutrophils release a variety of products that cause acute injury to alveolar capillary endothelial and epithelial lining cells.

This results in classic findings of DAD including increased vascular permeability, loss of diffusion capacity, necrosis of type II pneumocytes leading to surfactant loss, sloughing of surface epithelium, and leaking of proteinaceous fluid (exudate) into the alveoli, producing hyaline membranes.

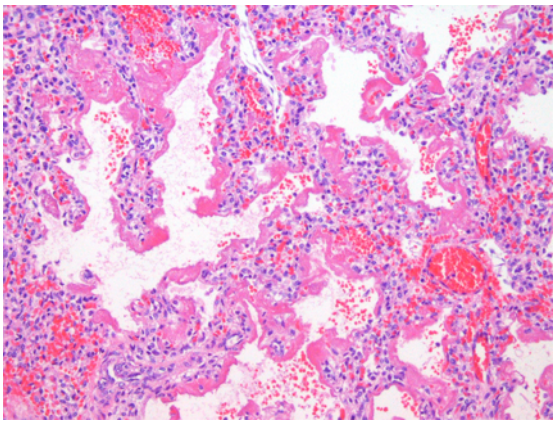
Morphology

Gross: heavy dark red, airless lungs

Microscopic: Diffuse alveolar damage is the histologic pattern encountered with ARDS. There is temporally uniform acute lung injury - edema, inflammation and fibrin deposition. Classically divided into 2 histologic phases

Acute stage (image): 1) Intra-alveolar edema and 2) hyaline membrane formation.

Organizing stage: 3) Proliferation of type 2 pneumocytes and finally 4) progressive interstitial fibrosis.



Clinical Course

Occurs 1-3 days after the initial insult (in 85% of patients). The patients present with profound dyspnea, hypoxemia and respiratory failure. Prognosis is poor with 60-70% mortality. If patients survive, post-ARDS fibrosis may occur, leading to chronic pulmonary disease. Some survivors regain their baseline lung function in 6-12 months.

Chronic restrictive / diffuse interstitial lung diseases

Overview

Heterogeneous and largely unrelated group of rare lung diseases characterized by chronic and diffuse involvement of lung connective tissue resulting in reduced compliance/scarring, which manifests as dyspnea and hypoxia. Surgical lung biopsy is the gold standard for the diagnosis. Even with open lung biopsies, correlation of the clinical, radiologic, and histologic features is critical for accurate classification. The various histologic patterns seen in these disorders are distinct, but not specific. The same histology may be seen not only in the idiopathic setting, but also in a variety of known etiologies. End stage, irrespective of etiology, is diffuse interstitial fibrosis with/without honeycombing (see "UIP" below).

Pathogenesis

Repeated cycles of acute lung injury and wound healing ultimately lead to widespread fibrosis and loss of lung function. Activated macrophages secrete chemo-attractants (IL-8) that activate neutrophils, which release mediators that injure alveolar epithelial cells and connective tissue. Macrophages also secrete mediators of wound healing (TGF-β) that cause fibrosis.

Major Categories

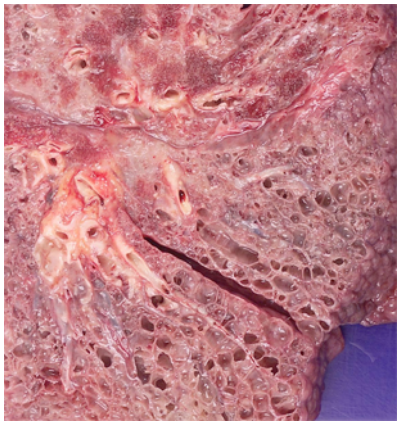
i. Fibrosing Diseases
    1. Idiopathic pulmonary fibrosis (IPF)
    2. Nonspecific interstitial pneumonia (NSIP)
    3. Cryptogenic organizing pneumonia (formerly "BOOP")
    4. Pneumoconioses such as coal workers' pneumoconiosis, silicosis, asbestosis
ii. Smoking-related disorders
    1. Desquamative interstitial pneumonia
    2. Respiratory bronchiolitis
iii. Granulomatous disorders
    1. Sarcoidosis
    2. Hypersensitivity pneumonitis
iv. Eosinophilic disorders

FIBROSING DISEASES

Idiopathic pulmonary fibrosis (IPF)

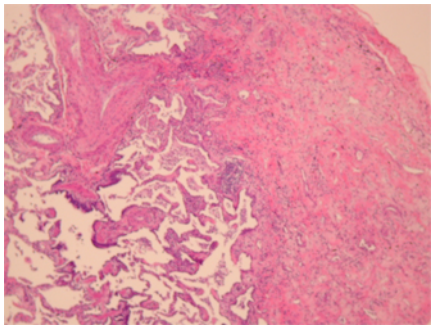
Introduction: It is the most common form of interstitial lung disease (55%). It is characterized by insidious onset and slow inexorable progression and marked interstitial fibrosis.

Etiology: Unknown



Clinical Features: Older population (60 yrs and older), Men>women (1.5-1.7:1)

Pathology:
Gross: The lung surface shows cobblestone appearance created by retraction of scar tissue along the interlobular septa. Cut surface shows a fibrotic, compressed parenchyma, more severe in the lower lobes and in subpleural and interlobular septal regions. Dilated air spaces alternate with the fibrous scar bands.



Microscopic: The pattern of changes seen microscopically by the pathologist is referred to as Usual Interstitial Pneumonia (UIP). The main microscopic findings for UIP include patchy (heterogeneous) interstitial fibrosis with subpleural accentuation which varies in intensity and chronicity (temporal heterogeneity), formation of cystic spaces, and variable interstitial lymphocytic infiltrates. A similar pattern of lung injury may be seen in cases of asbestosis and rheumatoid lung disease.

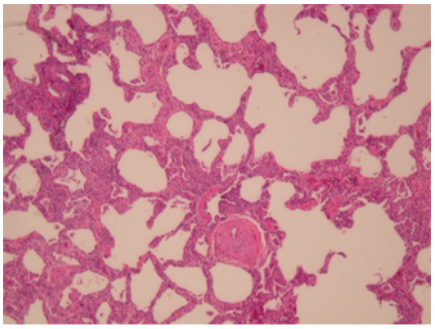
Clinical course: Gradual progressive course with increasing dyspnea, dry cough, hypoxemia, and respiratory failure. 5 year survival is 20%. Lung transplantation is the only definitive therapy. Pirfenidone (antifibrotic) and nintedanib (Tyrosine kinase inhibitor) have been recently approved for treatment of IPF. These slow down the progression of disease but do not reverse the disease.

Nonspecific interstitial pneumonia (NSIP)

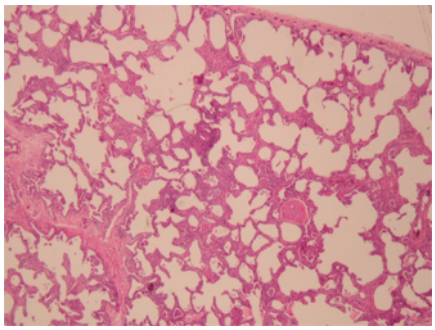
Introduction: introduced as a "waste basket" term to include all interstitial lung disorders of unknown etiology that do not fit other well-defined categories of interstitial lung disease. It is important to recognize because patients with NSIP usually have a better prognosis than those with UIP.

Clinical: - Age: 46-55 years. Dyspnea and cough for several months.

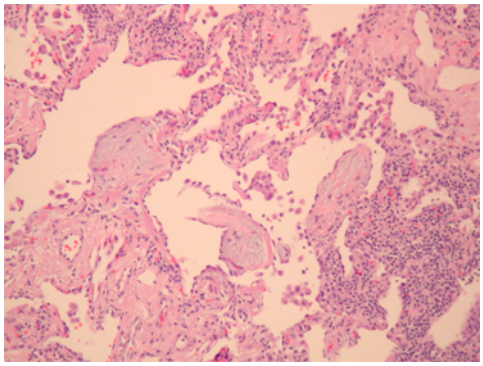
Pathology: - temporally uniform interstitial inflammation and fibrosis.



Cryptogenic organizing pneumonia (formerly Brochiolitis obliterans - organizing pneumonia; "BOOP")



COP represents a common response to infectious or inflammatory injury to lungs. It is characterized by temporally uniform polypoid masses of myxoid fibroblastic tissue in peripheral airways and alveoli. Diagnosis is made by lung biopsy. Treatment is steroids for long periods, with full recovery in most patients.



Pneumoconioses

Introduction: Non-neoplastic lung reaction to inhalation of mineral dusts, organic and inorganic particulates, chemical fumes, and vapor. Most of the pneumoconioses result from well-defined occupational exposure to airborne agents. The three most common are from exposure to coal dust, silica, or asbestos.

Pathogenesis

The development of pneumoconiosis is dependent on amount of dust retained in the lungs, which depends on variables such as size, shape, solubility, and reactivity of the dust particles. The dust concentration, duration of exposure, and effectiveness of clearance mechanism also determine the amount of dust retained in the lungs. Pulmonary macrophages are key in initiating and perpetuation of lung injury and fibrosis. Tobacco smoking worsens the effects of all inhaled mineral dusts, especially asbestos.

Different types of pneumoconioses

Coal workers' pneumoconiosis (CWP)

Introduction: Is defined as accumulation of coal dust in the lungs with associated tissue reaction. It is thought to take at least 10 years of exposure before manifesting.

a. Asymptomatic anthracosis
    i. Carbon-induced pulmonary lesion commonly seen in urban dwellers and smokers.
    ii. Carbon pigments are engulfed by macrophages in the lungs and accumulate in the connective tissue without significant reaction.
b. Simple CWP
    i. Coal dust macules (less than 1cm) consisting of carbon-laden macrophages and nodules containing small amount of collagen fibers are scattered throughout the lung especially in upper lobes.
    ii. Caplan's syndrome: CWP associated with Rheumatoid arthritis
c. Complicated CWP/ Progressive massive fibrosis
    i. Occurs in a background of simple CWP and generally requires years to develop and produces increasing pulmonary dysfunction
    ii. Intensely blackened scar larger than 2 cm
    iii. Microscopically, lesions consist of dense collagen and carbon pigment
    iv. No increased risk of bronchogenic carcinoma
    v. Unlike simple pneumoconiosis, which is nonprogressive after removal from dust exposure, PMF may appear long after exposure has ceased, and the lesions tend to enlarge with time.

Silicosis

Introduction: Fibrotic interstitial lung disease caused by inhalation of dust containing silicon dioxide (silica). It is the most prevalent chronic occupational lung disease. Hard rock miners, sandblasters, and pottery workers are at greatest risk

Pathogenesis: There are two forms of silica- crystalline and amorphous forms. Crystalline forms (quartz) are more toxic.

Morphology: Exposure leads to a variety of pathologic lesions (silicotic nodules, progressive massive fibrosis, silica proteinosis, diffuse interstitial fibrosis).
Silicotic nodules are classic lesions of silicosis- multiple, discrete, hard, pale to blue to green nodules primarily in the upper zone of the lungs. Central necrosis may be seen in cases of superimposed tuberculosis. Microscopically, they are sharply demarcated and composed of concentric hyalinized collagen with dust laden macrophages in the periphery. These may progress to progressive massive fibrosis (PMF) with coalescent areas of scar. "Egg shell" calcification may be seen in sclerosed hilar lymph nodes (nonspecific finding; also seen in other chronic conditions). Silicosis should not be diagnosed unless parenchymal silicotic nodules are present.

Clinical features:
a. Generally occurs after 20 years or more of exposure but can occur earlier if exposed to dusts of higher quartz content.
b. Associated with increased susceptibility to tuberculosis (2- 30 times higher)
c. Relation to lung cancer is controversial

Asbestos-related disease

Introduction: Asbestos is a family of crystalline hydrated silicates with fiber-shaped geometries. Occupational exposure to asbestosis (seen in mining and shipping industry) is linked to the following lung diseases:

Benign pleural lesions

1. Pleural plaque
2. Pleural effusion

Benign lung parenchymal lesions

3. Parenchymal interstitial fibrosis /asbestosis

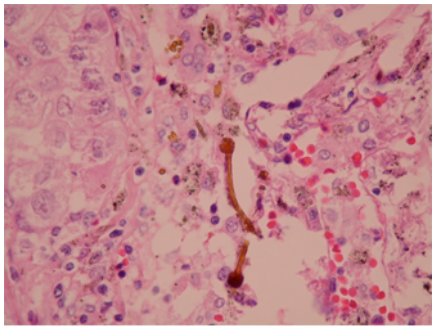
Neoplasms

4. Bronchogenic carcinoma
5. Mesothelioma
6. Laryngeal carcinoma

Pathogenesis:

a. Two distinct geometric forms: serpentine (flexible) and amphibole (stiff); both cause asbestos related diseases.
b. Serpentine chrysotile is more prevalent; however, amphibole is more pathogenic.

Morphology

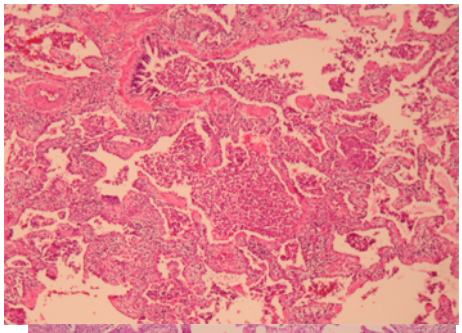


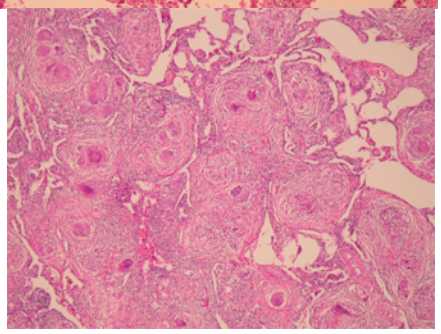
Asbestosis: A form of diffuse pulmonary fibrosis. The pattern of fibrosis is similar to that seen in UIP (lower lobes and subpleural).
Presence of asbestos bodies (aka ferruginous bodies) – golden brown fusiform or beaded rods with, translucent centers – is indicative of exposure. Asbestos bodies are asbestos fibers coated with iron-containing proteinaceous material.
Pleural plaque: Most common manifestation of asbestos exposure; characterized by well-circumscribed plaques of dense collagen in parietal pleura or diaphragm. They are merely markers of exposure and cause no clinical disease. They are not precursor lesions for mesothelioma. They do not contain asbestos bodies.

Smoking-related interstitial disease

Gradual onset of dyspnea and dry cough in chronic smokers. Two common morphologic forms include-

a. Desquamative interstitial pneumonia (DIP) - diffuse accumulation of pigmented macrophages (with iron deposition) in alveolar spaces and mild interstitial fibrosis.
b. Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD): the above changes are patchy and have a bronchocentric distribution.





Both these entities have an excellent response to steroids and cessation of smoking. They may represent different points along a spectrum of smoking related interstitial lung disease.

Granulomatous diseases

Sarcoidosis

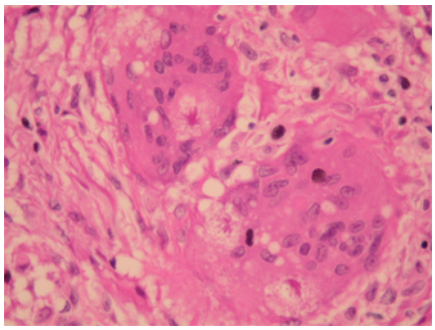
Introduction: Sarcoidosis is a relatively common systemic granulomatous disease commonly involving lungs and mediastinal lymph nodes. It is a multisystem disease of uncertain etiology characterized by non-necrotizing granulomas in many organs. It is a diagnosis of exclusion. Some common differential diagnoses that should be excluded are mycobacterial and fungal infections and berylliosis.

Etiology: unknown. It is thought to be due to cell-mediated response to an unidentified antigen and driven by CD4+ helper T cells.

Clinical features:
It is common in younger adults (< 40), with a higher incidence in African-Americans and in non-smokers. Patients may be asymptomatic with incidental abnormal X-ray. Bilateral hilar lymphadenopathy with/without lung involvement is highly suggestive of sarcoidosis. Lung is the most common site of involvement (90%). Other organs involved are lymph nodes (75-90% cases), skin (erythema nodusum), heart (conduction system abnormalities), spleen, liver, CNS (especially involvement of cranial nerve VII causing paralysis of facial muscles), bone marrow, and eyes (iritis, irdiocyclitis, and uveitis). Clinical course is unpredictable and may be characterized by progressive chronicity or periods of activity interspersed with remission. Overall 65-70% of the patients recover. Progressive pulmonary fibrosis and cor pulmonale develop in some.

Important lab features:
May have elevated angiotensin converting enzyme (ACE) levels. This is not specific but it helps in monitoring the clinical response to steroid therapy.
Hypercalcemia (mononuclear cells produce active vitamin D).
Decreased circulating CD4+ lymphocytes.

Pathology: Non-necrotizing well formed 'tight' or 'naked' granulomas, with Langhans or foreign body type giant cells and a thin rim of lymphocytes (or no lymphocytes), are the hallmark of this disease.
Granulomas are distributed in the lung interstitium along lymphatics and bronchioles.
Two other (nonspecific) histologic features that may sometimes be seen:



1. Schaumann Bodies: laminated concretions composed of calcium and proteins
2. Asteroid bodies: eosinophilic stellate inclusions within giant cells

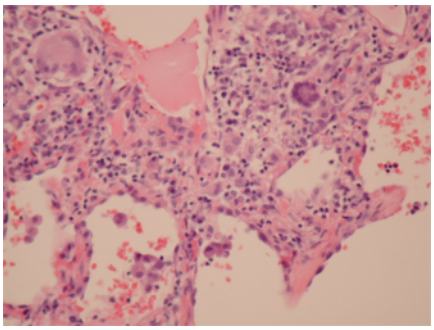
Hypersensitivity pneumonitis

Introduction: HP is a prototypic interstitial lung disease of *known* etiology. It is important not to miss this diagnosis, since reducing exposure to the inciting agent is important for treatment. It may present as an acute event or as a chronic disease.

Etiopathogenesis: Immunologically mediated (type III and IV hypersensitivity) interstitial lung disorder caused by hypersensitivity to inhaled organic dust antigens such as moldy hay. The various forms are named after the offending occupational allergen, for e.g.:

i. Farmer's lung results from exposure to thermophilic actinomycetes generated from harvested humid, warm hay
ii. Pigeon breeder's lung caused by inhalation of proteins derived from excreta or feathers of birds
iii. Humidifier or air conditioner lung caused by thermophilic bacteria in heated water reservoirs

Pathology:
Patchy lymphocytic infiltrate with peribronchial accentuation and mild fibrosis. Interstitial non-necrotizing granulomas can often be seen. May rarely progress to endstage fibrosis/honeycomb lung.



Eosinophilic diseases (Not covered in lecture)

a. Acute eosinophilic pneumonia with respiratory failure
b. Simple pulmonary eosinophilia (Loffler syndrome)
c. Tropical eosinophilia
d. Secondary eosinophilia
e. Idiopathic chronic eosinophilic pneumonia

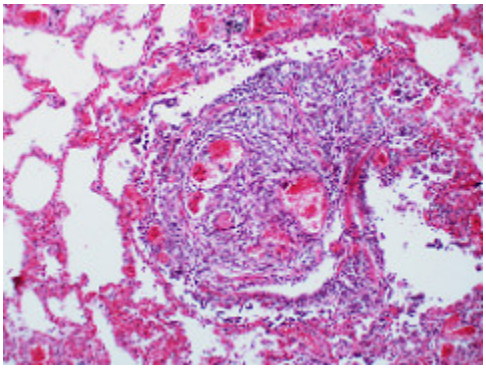
Vascular diseases

Pulmonary hypertension

Introduction: Mean pulmonary arterial pressure ≥ 25 mmHg (normal <20 mmHg)

WHO Classification of Pulmonary Hypertension :
Group 1 : Pulmonary arterial hypertension (rare) : can be idiopathic, secondary to connective tissue disease, drugs, HIV or sickle cell disease
Group 2 : Most common form. Pulmonary venous hypertension due to left heart disease.
Group 3 : Due to Lung disease : obstructive or interstitial lung disease
Group 4 : Chronic thromboembolic pulmonary hypertension : Due to incomplete resolution of pulmonary emboli.
Group 5 : Unclear multifactorial mechanisms

Pathogenesis:
In secondary pulmonary hypertension there is pulmonary endothelial or vascular smooth muscle dysfunction produced by mechanical injury due to increased blood flow. This leads to decreased production of vasodilators (prostacyclin and nitric oxide) and increased release of vasocontrictors (endothelin). Production of and release of growth factors and cytokines induce migration and replication of vascular smooth muscle cells.



Primary pulmonary hypertension may be secondary to TGF-β pathway abnormality. Germ line mutation of bone morphogenetic protein receptor type 2 (BMPR2) has been demonstrated.

BMPR2 is a cell surface protein that binds several cytokines. BMPR2 signaling causes inhibition of proliferation. In the absence of BMPR2 signaling, proliferation of smooth muscle leads to vascular thickening and occlusion, leading to pulmonary hypertension.

Morphology
All forms of pulmonary hypertension have some common features, including medial hypertrophy and atheroma formation. Plexiform lesions (image) – tufts of capillary formation filling the lumens of arteries – can be seen in some cases of severe PH, especially idiopathic familial PH, unrepaired congenital heart disease with left-to-right shunts, and PH associated with drugs and HIV.

Diffuse alveolar hemorrhage syndromes
Introduction: Group of primary immune mediated diseases with a triad of hemoptysis, anemia, and diffuse pulmonary infiltrates

Goodpasture Syndrome: Hemorrhagic interstitial pneumonitis and glomerulonephritis. The pathology in the lung consists of consolidated areas of intra-alveolar hemorrhage and the presence of hemosiderin (free or in macrophages) within alveoli. Fluorescent microscopy shows a linear immunoglobulin deposition along alveolar septa.

Idiopathic Pulmonary Hemosiderosis: Mostly affects children. Unknown etiology. Pathologically similar to Goodpasture syndrome but there is no renal involvement and no immunoglobulin deposition. Usually has a milder course with full remission.

Wegener's granulomatosis: Systemic necrotizing vasculitis involving upper and lower respiratory tracts and glomerulonephritis. Lung disease is characterized by necrotizing vasculitis (inflammation and fibrinoid necrosis) and parenchymal granulomatous inflammation. Antineutrophil cytoplasmic antibodies (c-ANCA) are detected in 90% of patients.